Research Involving Human Subjects and/or Anatomical Substances

This appendix contains the required approvals, forms, and descriptions for research involving human subjects and/or human anatomical substances (including human organs, tissues, cells, body fluids from human subjects as well as graphic, written, or recorded information derived from human subjects). Specific guidelines are subject to change as governing regulations, policies, and procedures are updated.

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Research Involving Human Subjects and/or Anatomical Substances

1. Introduction

In 1991, the Department of Defense (DOD), together with 15 other federal agencies, adopted regulations that are known collectively as the Common Federal Rule. These regulations embody the ethical principles of the Belmont Report. Title 32 Code of Federal Regulations Part 219 (32 CFR 219), "Protection of Human Subjects" applies to all research involving human subjects conducted or supported by the DOD. The Department of Health and Human Services (DHHS) National Institutes of Health (NIH) corollary is 45 CFR 46. Research conducted or funded by the U.S. Army Medical Research and Materiel Command (USAMRMC) is also governed by Army Regulation (AR) 70-25, January 1990 and Office of The Surgeon General (OTSG) Regulation 15-2, January 1989. The USAMRMC also adheres to the Food and Drug Administration (FDA) regulation, Title 21 Code of Federal Regulations for research involving investigational drugs or devices. The OTSG maintains the overall responsibility for protecting human research subjects for the Department of the Army.

2. Definitions

2-a. Research

In the Common Federal Rule, research is defined as " . . . a systematic investigation, including research development, testing and evaluation designed to develop or contribute to generalizable knowledge" (32 CFR 219.102). Activities that meet this definition constitute research for purposes of this policy, whether they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities.

The FDA defines clinical investigation as " . . . any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects" (21 CFR 312.3). This definition applies to research involving the use of FDA-regulated products.

2-b. Human Subjects

In the Common Federal Rule, a human subject is defined as "a living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information" (32 CFR 219.102).

The FDA defines a human subject as "an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient" (21 CFR 312.3).

2-c. Human Anatomical Substances (and Privileged or Protected Health Information)

The Common Federal Rule applies to the use of human organs, tissues, cells, or body fluids from individually identifiable human subjects and graphic, written, or recorded information derived from individually identifiable human subjects.

3. Human Subjects Research Review Board

3-a. Review Levels for DOD-Sponsored Research

In addition to first level of review and approval by the local Institutional Review Board (IRB), a second level of review and approval is required for DOD-sponsored research. If a research proposal is recommended for funding and the research involves human subjects, human anatomical substances, or privileged or protected health information, a research protocol must be submitted to the Human Subjects Research Review Board (HSRRB) for review and approval. HSRRB approval must be obtained prior to initiation of the research protocol. The HSRRB is functionally similar to a civilian IRB. The HSRRB is supported administratively by the Office of Regulatory Compliance and Quality, USAMRMC.

If a claim of exemption is submitted, the Acting Chair of the HSRRB will review the protocol and make a determination of exempt status.

If the local IRB has made an assessment that the proposed research is no greater than minimal risk (NGTMR) and the research is eligible for expedited review, the Acting Chair of the HSRRB will review the protocol. If the protocol is not eligible for expedited review, it will receive a full HSRRB review at a convened Board meeting.

If the local IRB has made an assessment that the proposed research is greater than minimal risk (GTMR), the protocol will receive a full HSRRB review. The protocol must be submitted through the Office of Regulatory Compliance and Quality to the HSRRB for full review and approval prior to initiation of the research.

3-b. Timelines and Outcomes

Initial feedback from the HSRRB is given to the principal investigator within 1 month after submission of a complete protocol packet. After the protocol is approved, any revisions to the protocol, consent form, advertisements, questionnaires, or other related study documentation must be submitted through the local IRB to the HSRRB for approval prior to implementation. The Surgeon General (TSG) of the U.S. Army must approve the recommendations of the HSRRB. The HSRRB will make one of the following recommendations to TSG:

Approval. The protocol should be approved without further revisions.

Conditional Approval. Approval of the protocol is contingent upon revisions being made and/or additional information being provided. The principal investigator should address the Board's recommendations and submit a revised protocol and related documents to the Acting Chair, who can approve the revised protocol when all of the Board's recommended revisions and requests for additional information have been adequately addressed.

Disapproval. A protocol is not approved when there are substantive concerns about the conduct of the protocol and/or safety of the subjects. The principal investigator should address the Board's recommended revisions and requests for additional information and submit a revised protocol and related documents to the Acting Chair for review at another convened meeting of the HSRRB.

Deferral. A protocol may be deferred or tabled for action at another meeting when there is a lack of sufficient information to make a more definitive recommendation.

3-c. Multi-site Protocol Review

For multi-site protocols involving the use of human subjects, the protocol and consent form for the primary site are first reviewed and approved by expedited or full Board review as appropriate. If the same protocol used by the primary site will be used at each of the other sites, each site-specific consent form can receive expedited review after review and approval of the protocol and consent form for the primary site. In addition, all domestic and foreign sites are required to assure compliance with the federal policy for the protection of human subjects. If an awardee institution or any of the collaborating sites does not have an assurance number, such as a Multiple Project Assurance (MPA) with the DHHS Office for Human Research Protections, then an application for a DOD single project assurance (SPA) must be completed by each site that does not have an assurance and the application must be submitted to the Human Subjects Protection Branch of the USAMRMC. Refer to part 12, "Assurances" in this appendix for further details regarding submission of an SPA application.

4. Claim of Exemption

4-a. Approval of Exempt Status for Research Involving Human Subjects or Anatomical Substances

Certain categories of research are exempt from review by the HSRRB in accordance with federal guidelines. If your research fits in one or more of these categories, you may request exempt status for your protocol. Your protocol and Claim of Exemption form will be reviewed to evaluate your claim of exemption.

4-b. Exempt Categories

The following list taken from 32 CFR 219.101 details the exemption categories.

1. Research conducted in established or commonly accepted educational settings involving normal educational practices, such as:

   a. research on regular and special education instructional strategies, or

   b. research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless:

   a. information obtained is recorded in such a manner that human subjects can be identified directly or through identifiers linked to the subjects; and

   b. any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph 2 of this section, if:

   a. the human subjects are elected or appointed public officials or candidates for public office, or

   b. federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

4. Research involving the collection or study of existing data, documents, records, pathological specimens or diagnostic specimens, if these sources are publicly available of if the information is recorded by the investigator in such a manner that subjects cannot be identified directly or through identifiers linked to the subjects.

5. Research and demonstration projects that are conducted by or subject to the approval of Department or Agency heads, and that are designed to study, evaluate, or otherwise examine:

   a. public benefit or service programs,

   b. procedures for obtaining benefits or services under those programs,

   c. possible changes in or alternatives to those programs or procedures, or

d. possible changes in methods or levels of payment for benefits or services under those programs.

6. Taste and food quality evaluation and consumer acceptance studies,

   a. if wholesome foods without additives are consumed, or

   b. if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

4-c. Claiming Exemption

Investigators who believe that their protocol is exempt from review should submit (1) a completed Claim of Exemption Form and (2) documentation from the local IRB stating that the protocol has been determined to be exempt.

5. Minimal Risk Research

5-a. Approval of NGTMR Research Involving Human Subjects or Human Anatomical Substances

Minimal risk is defined as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests" in 32 CFR 219.102(i). If the research protocol is assessed as minimal risk in accordance with this definition and regulation, it can be approved by expedited review if the study involves one of the research categories that qualifies for expedited review, as listed in the Federal Register, Notices, Vol. 63, No. 216, dated November 9, 1998. For example, the following is a brief synopsis of these categories:

1. Clinical studies of drugs for which an Investigational New Drug (IND) application is not required or of medical devices for which an Investigational Device Exemption (IDE) application is not required or the medical device has been cleared/approved for marketing and the device is being used for its cleared/approved labeling.

2. Collection of blood samples by finger, heel or ear stick, or by venipuncture, where the amount of blood drawn does not exceed 550 mL in an 8-week period and collection does not occur more frequently than two times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means, such as hair and nail clippings, teeth extracted as routine patient care, excreta and external secretions, saliva, placenta removed at delivery, amniotic fluid obtained at the time of membrane rupture or during labor, dental plaque and calculus that is not more invasive than routine care, mucosal and skin cells collected by buccal scraping, mouthwashings or swab, and sputum.

4. Collection of data through noninvasive procedures not involving general anesthesia or sedation.

5. Research involving materials, such as data, documents, records or specimens, that have been collected or will be collected solely for nonresearch purposes (e.g. medical treatment or diagnosis).

6. Collection of data from voice, video, digital or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior, or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation or quality assurance methodologies.

8. Continuing review of previously approved research.

5-b. Approval of a NGTMR Research Study with a Waiver of Informed Consent

A minimal risk protocol approved by expedited review can have the requirement for a written informed consent document waived if it meets the following four criteria, as outlined in 32 CFR 219.116(d):

1. The research involves no more than minimal risk to the subjects.

2. The waiver or alteration will not adversely affect the rights and welfare of the subjects.

3. The research could not practicably be carried out without the waiver or alteration.

4. Whenever appropriate, the subjects will be provided with additional information after participation.

If the local IRB has approved a protocol with waiver of informed consent and the study includes use of human anatomical substances, submit a copy of the consent form used to document individuals' consent to use their tissue, blood, or other medical information or records for research purposes.

6. Training for Research Investigators

Research investigators must complete appropriate institutional training before conducting human subjects research. Documentation of the most recent ethics training must be submitted for all investigators and other research staff for all protocols. In addition, for all investigational drug and device protocols, documentation of successful completion of a course in the conduct of clinical research in accordance with Good Clinical Practices (GCP) must be submitted for all investigators and other research staff. The most recent ethics training and GCP course must be successfully completed within one year of the planned initiation of the protocol.

7. Guidelines for Writing Research Protocols Involving Human Subjects

7-a. Title 10 United States Code 980 (10 USC 980)

Before writing the research protocol, investigators must consider the requirements of 10 USC 980, which are applicable to DOD-sponsored research. 10 USC 980 requires that "Funds appropriated to the Department of Defense may not be used for research involving a human being as an experimental subject unless (1) the informed consent of the subject is obtained in advance, or (2) in the case of research intended to be beneficial to the subject, the informed consent may be obtained from a legal representative of the subject." **Furthermore and consistent with the Common Federal Policy for the Protection of Human Subjects, if an individual cannot give his or her own consent to participate in a research study, consent of the individual's legally authorized representative must be obtained prior to the individual's participation in the research. Moreover, an individual not legally competent to consent (e.g., incapacitated individuals, incompetents, minors) may not be enrolled in DOD-sponsored research unless the research is intended to benefit each subject enrolled in the study. For example, a subject may benefit directly from medical treatment or surveillance beyond the standard of care. Proposers should be aware that this law makes placebo controlled clinical trials problematic because of the 'intent to benefit' requirement whenever participation is sought of subjects from whom consent must be obtained by the legally authorized representative.**

7-b. Protocol Format

A detailed research protocol must be submitted for all protocols, including IND or IDE protocols, for human subjects protection review. In addition, the protocol must be reviewed and approved by the local IRB of Record before it can be reviewed by the HSRRB, and the approval letter from the local IRB must be submitted with the protocol for initial HSRRB review.

IND or IDE protocols will follow the format described in the International Conference on Harmonisation (ICH), Consolidated Guideline E6 (http://www.ifpma.org/pdfifpma/e6.pdf). Other protocols may follow the ICH Guideline and include applicable paragraphs.

7-c. Required Elements of the Protocol

1. Protocol Title. The protocol title must be the same as the project/proposal title unless multiple protocols are being submitted within one proposal.

2. Phase. For medical products regulated by the Food, Drug, and Cosmetic Act, designate the protocol as Phase I, II, III, or IV research.

3. Principal Investigator. List the complete name, address, phone number, and email address of the principal investigator. Include a copy of the principal investigator's curriculum vitae (CV) with the protocol. List the names of all personnel who will have significant involvement in the research study; include their practice license (i.e., MD or RN), highest degree(s), job title, and employing institution. In addition, if a Medical Monitor has been

assigned to the study, which is required only for greater than minimal risk studies, include his/her name and provide a copy of the current CV.

4. Location of Study. List all centers, clinics, or laboratories where the study is to be conducted. Include the name, degree(s), title, employing institution, and complete address of the investigator(s) for each site.

5. Time Required to Complete. State the month and year of expected start and completion times.

6. Objectives. Provide a detailed description of the purpose and objectives of the study.

7. Study Population.

    a. Describe the target population (to whom the study findings will be generalized) and the nature, approximate number, and pertinent demographic characteristics of the accessible population at the study site (population from which the sample will be recruited/drawn).

    b. Describe the methods that will be used to obtain a sample of subjects from the accessible population (i.e., convenience, simple random, stratified random) together with the inclusion and exclusion criteria (include age, gender, ethnicity).

    c. If pregnant subjects will be excluded from participation in the study, the method used to determine pregnancy status in women of childbearing potential must be specified. Also, state the time that will elapse between the pregnancy test and exposure to research procedures or medical products and how long the non-pregnant subject should use effective contraceptive practices after participating in the study. Please note that contraceptive practices may be necessary for male subjects participating in certain types of studies. For IND studies, pregnancy testing is required within 48 hours before the start of the study.

8. Protocol Design. Outline the proposed methodology in sufficient detail to show a clear course of action. Technological reliability and validity of procedures should be indicated. Minimum guidance for the plan should include:

    a. Subject identification. Describe the code system to be used.

    b. Description of the recruitment process. Describe who will identify potential subjects, who will recruit them, and how they will be recruited. Provide copies of all recruitment and advertisement materials for review.

    c. Description of the Informed Consent process. Specifically describe the plan for the informed consent process by stating who will perform the informed consent interview, when the interview will take place relative to the participant beginning study participation and in relation to any stressful situation like being informed s/he has cancer, or in relation to the administration of any mind-altering substances such as tranquilizers, conscious sedation, or anesthesia. Address how privacy and time for decision-making will be provided and whether

or not the potential subject will be allowed to discuss the study with anyone before making a decision. Indicate who will serve as the witness to the informed consent interview. Please note that a witness is required to be present during the informed consent interview. Two copies of the consent form should be completed so that the subject can get an original copy and a copy can be kept for the PI's study records. A third copy may be needed for the patient's medical record; check with the participating site for specific study-site requirements.

d. Subject assignment (randomization).

e. Evaluations prior to entry. List and describe any evaluations (e.g., laboratory procedures, history, or physical examination) that are required to determine eligibility/suitability for study participation. Please note that some screening procedures may need a separate consent or a two-stage consent process.

f. Evaluations to be made during the conduct of the study (e.g., laboratory evaluations, specimens to be collected, schedule and amounts, storage to include where and whether special conditions are required, labeling, and disposition). For studies using multiple measures or tests over time, it is helpful to display the data collection schedule in a spreadsheet or tabular format.

g. Clinical assessments (e.g., schedule of clinical evaluations and follow-up procedures). Provide a copy of all case report forms, data collection forms, questionnaires, rating scales, and/or interview guides that will be used in the study.

h. Describe the research intervention or activity that the subject will experience. Provide sufficient detail in chronological order for a person uninvolved in the research to understand what the subject will experience.

9. Risks/Benefits Assessment.

   a. Describe risks (physical [including pain and discomfort, disfigurement, infection, injury, death], psychological, social, economic, legal, and privacy/confidentiality risks]) associated with the research, measures to be taken to minimize and/or eliminate risks or to manage unpreventable risks and special medical or nursing care that will be needed prior to, during, or following participation.

   b. Describe benefits of the research to the subject. If there will be no benefits to the subjects (other than knowing s/he has contributed to science), state this in the protocol and consent form.

   c. Payment or compensation for participation is not considered to be a benefit and must be addressed in a separate section.

10. Reporting of serious or unexpected adverse events.

    a. Serious or unexpected adverse events can occur in any and all types of studies, not just experimental interventions or clinical trials.

b. Include a definition of what constitutes an adverse event in the study.

(1) For IND or IDE research, include definitions as described in 21 CFR 312.32.

(2) All research protocols must address the following requirements, which is language from HSRRB Clause 7.01:

"An adverse event temporarily related to participation in the study should be documented whether or not considered to be related to the test article. This definition includes intercurrent illnesses and injuries and exacerbations of preexisting conditions. Include the following in all IND safety reports: Subject identification number and initials; associate investigator's name and name of MTF; subject's date of birth, gender, and ethnicity; test article and dates of administration; signs/symptoms and severity; date of onset; date of resolution or death; relationship to the study drug; action taken; concomitant medication(s) including dose, route, and duration of treatment, and date of last dose."

c. Describe agencies or offices to be notified with point of contact information in the event of a serious and unexpected adverse event. For all protocols involving human subjects, including investigational new drug or device studies, the following information about reporting serious and unexpected adverse events, which is language from HSRRB Clause 1.02, must be included in the protocol:

"Adverse experiences that are both serious and unexpected will be immediately reported by telephone to the USAMRMC, Deputy for Regulatory Compliance and Quality (301-619-2165) and send information by facsimile to 301-619-7803). A written report will follow the initial telephone call within 3 working days. Address the written report to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, Maryland 21702-5012."

11. Description of Protocol Drugs or Devices. If the protocol uses an investigational drug or device, provide the following information:

a. IND/IDE number and name of sponsor.

b. Complete names and composition of all medication(s), device(s), or placebo(s).

c. Source of medications, devices, or placebos.

d. Location of storage for study medications.

e. Dose range, schedule, and administration of test articles.

f. Washout period, if used, should be described in detail.

g. Duration of drug or device treatment.

h. Concomitant medications allowed.

i. Antidotes and treatments available.

j. Disposition of unused drug.

k. The procedure by which the IND sponsor will monitor the protocol in accordance with 21 CFR 312.

(1) In addition to the above list of requirements to address in the protocol, include the following with the protocol submission:

(a) A copy of the Investigator's Brochure and/or device manual and associated case report/data collection forms.

(2) A signed Form FDA 1572 for IND Applications that have been approved by the FDA, including the following information (for non-FDA new drug protocols, the following information should be included in the protocol):

(a) Name, address and a statement of the qualifications for each investigator and the name of each sub-investigator working under the PI.

(b) Names and addresses of facilities to be used.

(c) Name and address of each IRB reviewing the protocol.

(3) For Investigational Devices, include your local IRB's assessment of the risk, such as nonsignificant or significant risk, of the investigational device you plan to use in your study. If the device poses significant risk to research subjects, specify the IDE number obtained from the FDA, the name of the sponsor, and the procedure by which the IND sponsor will monitor the protocol in accordance with 21 CFR 812.

12. Disposition of Data. Describe where data will be stored, who will keep the data, how the data will be stored and the length of time data will be stored. Note that records of IND studies must be kept until 2 years after a New Drug Application is approved/issued, or for 2 years after the IND is withdrawn. Records required for IDE studies should be retained for 2 years after the latter of the following dates: the date that the investigation is terminated or completed and the date that the records are no longer required for support of the pre-market approval application. For studies with minors, most states require keeping records for up to 7 years (dependent on state's statute of limitations) past the subject's age of majority.

13. Modification of the Protocol. Describe the procedures to be followed if the protocol is to be modified, amended, or terminated before completion. Note that any modification to the

protocol, consent form and/or questionnaires must be submitted to both the local IRB and the HSRRB for review and approval. Address this procedure even if you do not anticipate making any modifications.

14. Departure from the Protocol. Describe procedures and notifications to be made in the event of deviations from the approved protocol requirements.

15. Roles and Responsibilities of Study Personnel. Briefly describe the duties of all study personnel, which should include each of the persons listed as investigators, research staff, consultants, and the medical monitor. Describe their roles in the research effort (e.g., Research Coordinator, 80%, recruit and consent subjects, maintain study records, administer study drug, take and record vital signs, enter data into computer data base). Duties of the medical monitor, as defined in HSRRB Clause 8.02, are as follows:

> A medical monitor must be assigned to greater than minimal risk protocols. The name and curriculum vitae of the medical monitor, who is someone other than the principal investigator, must be provided. This individual should be a qualified physician who is not associated with the protocol, able to provide medical care to research subjects for conditions that may arise during the conduct of the study, and able to monitor subjects during the conduct of the study. The medical monitor is required to review all serious and unexpected adverse events associated with the protocol and provide an unbiased written report of the event within 10 calendar days of the initial report. At a minimum, the medical monitor should comment on the outcomes of the adverse event and relationship of the event to the test article. The medical monitor should also indicate whether he/she concurs with the details of the report provided by the principal investigator.

The medical monitor will forward reports to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

16. Investigators conducting greater than minimal risk research must include the following description of requirements of the Volunteer Registry Database (HSRRB Clause 2.01) in the protocol and consent form:

> "It is the policy of USAMRMC that data sheets are to be completed on all volunteers participating in research for entry into the U.S. Army Medical Research and Materiel Command Volunteer Registry Database. The information to be entered into this confidential database includes name, address, social security number, study name, and dates. The intent of the database is twofold: first, to readily answer questions concerning an individual's participation in research sponsored by the USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at the USAMRMC for a minimum of 75 years."

Include in the protocol language to indicate that the Volunteer Registry Data Sheet must be completed. (See Parts 8 and 17 of this appendix.) In addition, include the completion of the

data sheets in the study procedure timelines. Once completed, the data sheets must be sent to the following address:

Commanding General, U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RCQ-HR
504 Scott Street
Fort Detrick, Maryland 21702-5012

These data sheets may be submitted annually and upon completion of the study. In addition, some facilities have the capability to enter the information directly and may continue to do so. Use of the Volunteer Registry Data Sheets is not required for exempt or no greater than minimal risk studies, unless otherwise indicated.

7-d. Advertisements, Posters, and Press Releases to Recruit Subjects

If subjects will be recruited through an advertisement, newspaper article, or similar process, a copy of the local IRB-approved advertisement must be provided.

For studies involving investigational drugs or devices, local IRB review of advertisements is necessary to ensure that the information is not misleading to the subjects participating in IND studies. The FDA has established guidelines on advertisements for subjects. General guidance includes name and address of PI, summary of research purpose, brief eligibility criteria, truthful list of benefits, and the person to contact for further information.

7-e. Surveys, Questionnaires, and Other Data Collection Instruments

If the research involves surveys, questionnaires, or other instruments, include a copy of the most recent IRB-approved version of each of these documents with the protocol submission. For either of these instruments that is used, the following information at a minimum should be addressed:

The instrument should be labeled with the complete title of the study and instructions for completing and returning the instrument. The instructions should state that the subject can refuse to answer specific items without repercussions. The instrument should be related to the objectives of the study.

Address whether the instrument has been validated.

The instructions and item order should be comprehensible and unambiguous.

Describe the procedure for confidentiality of hardcopy data or electronic data in the protocol and consent form.

8. Informed Consent Document Requirements

8-a. Required Elements of the Informed Consent Document

The format of the informed consent document may vary in accordance with the requirements of the local IRB. However, the informed consent document title must be the same as the protocol title. The following information is required for informed consent documents (32 CFR 219.116 and AR 70-25):

A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental.

A description of any reasonably foreseeable risks or discomforts to the subject.

A description of any benefits to the subject or to others, which may reasonably be expected from the research.

A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. For example, describe procedures that will be followed to maintain the subject's privacy and confidentiality, how the identifying information or specimens will be stored and for how long. Also describe who will have access to the identifying data.

For research involving greater than minimal risk, include the following explanation of medical care available for research-related injury:

"Should you be injured as a direct result of participating in this research project, you will be provided medical care, at no cost to you, for that injury. You will not receive any injury compensation, only medical care. You should also understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the principal investigator before you enroll in this study."

An alternative clause for medical care in the event of a research-related injury can be incorporated into the consent form and is as follows:

"This study is being funded by the Department of Defense and conducted by the United States Army. Army regulations provide that, as a volunteer in a study conducted by the United States Army, you are authorized all necessary medical care for any injury or disease that is a direct result of your participation in the research. The Principal Investigator or his designee will assist you in obtaining appropriate medical treatment under this provision if it is required. If you have any questions concerning your eligibility for Army funded medical treatment, you should discuss this issue thoroughly with the Principal Investigator or his designee before you enroll in this study. This is not a waiver or release of your legal rights."

Three possible mechanisms are available to offset the costs of this requirement:

a. The proposed recipient may absorb such costs into the institution's operating budget.

b. The proposed recipient's liability insurance, if available, may be sufficient to cover any medical care costs. The proposed recipient's business office and/or legal advisor must ensure that there is adequate coverage under this liability insurance.

c. The proposed recipient could negotiate an additional amount of funds, if available, into the award that will cover such medical care cost (such as liability insurance).

If private citizens are enrolled, the following statement should be added to the consent form with the medical care clause:

> "Other than medical care that may be provided and any other payment specifically stated in the consent form, there is no other compensation available for your participation in this research."

The name and contact information for someone to contact (a) about the research, (b) about research subjects' rights, and (c) about a possible research-related injury.

A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

8-b. Additional Elements of the Informed Consent Document

When appropriate, one or more of the following elements of information shall also be provided to each subject (32 CFR 219.116 and applicable state/local laws):

A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable.

Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

Any additional costs to the subject that may result from participation in the research.

The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
The approximate number of subjects involved in the study.

Documentation of consent for human immunodeficiency virus (HIV) antibody testing, if scheduled, may be addressed in the body of the consent form or as separate HIV test consent

form. Documentation should address any notifications required by state or local laws as well as any specific issues regarding confidentiality of positive test results.

The signature block of the consent form should include a signature line for the subject or legally authorized representative, lines for the permanent address of the subject, and separate lines for the printed name and signature of the witness. On every page of the consent form, except the signature page, include lines for the initials of the subject and the witness.

8-c. Requirements Unique to DOD-Sponsored Research

Certification of Translation

Provide documentation that the foreign language version of the consent form is an accurate translation. Documentation of translation must be provided along with the English and foreign language version of the consent forms. The documentation of translation should include the following statement, "I certify that this is an accurate and true translation" as well as the signature, name, address, phone number and, if available, fax number of the translator.

Sample Donation

If the samples donated in this study will be used in other studies, the following statement should be included in the consent form:

> "During this study, you will be asked to provide _____ (clearly specify the type of samples to be provided). These samples will be used for _____ (enter all known and anticipated uses) and may also be used for purposes that are currently unknown. There is a chance that the samples that you are donating under this study may be used in other research studies and may have some commercial value. (If a commercial value is anticipated, that value should be clearly described at this point.) Should your donated sample(s) lead to the development of a commercial product, _____ will own it and may take action to patent and license the product. _____ does not intend to provide you with any compensation for your participation in this study nor for any future value that the sample you have given may be found to have. You will not receive any notice of future uses of your sample(s). (When the study involves treatment as well as research, the following language should be added: You may agree to participate in the research protocol, but refuse to provide the additional samples discussed above.)."

In addition, a donation form may be prepared for signature by the volunteer and a witness that states:

> "As a participant in _____ (insert the title of the study), I voluntarily donate any and all _____ (clearly specify the type of sample(s) to be provided) to _____. These samples will be used for (enter all known and anticipated uses) and may also be used by _____ for uses not currently known to me. There is a possibility that the samples that I am donating under this study may be used in other research studies and may have some commercial value. (If a commercial value is anticipated, that value should be clearly described at this point). Should my donated sample(s) lead to the development of a commercial product, _____ will own it and it is possible that it will be patented and licensed by _____. _____

does not intend to provide me any compensation for this and will not give me any notice of future uses of my sample(s)."

Please note that a separate sample donation form is not required. If you choose not to draft a separate sample donation form, the language from the first paragraph of this clause must be included in the informed consent document.

Payment for Study Participation: Active Duty Military Personnel

Under 24 USC 30, payment to Active Duty military personnel for participation in research is limited to blood donation and may not exceed $50 per blood draw. Active duty research subjects may not receive any other payment for participation in a research study.

Confidentiality

The following statement must be included in the consent form for all protocols that enroll military personnel:

"All data and medical information obtained about you, as an individual, will be considered privileged and held in confidence; you will not be identified in any presentation of the results. Complete confidentiality cannot be promised to subjects, particularly to subjects who are military personnel, because information bearing on your health may be required to be reported to appropriate medical or command authorities."

For studies involving civilian subjects and their donated samples, include language describing how the subject's confidentiality will be maintained, how long the samples will be retained, and who will have access to the samples. In addition, include language from HSRRB Clause 11.01-Review of Research Records, which states:

"It should be noted that representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as a part of their responsibility to protect human subjects in research."

Pregnant Women

If pregnant women will be excluded, the following statement must be included if pregnancy during or after the study constitutes a risk to the participant or fetus:

"I should avoid becoming pregnant for at least (time period in days, weeks, or months) after participation in the study. To avoid becoming pregnant, I should either abstain from

sexual relations or practice a method of birth control. Except for surgical removal of the uterus, birth control methods such as the use of condoms, a diaphragm or cervical cap, birth control pills, IUD, or sperm-killing products are not totally effective in preventing pregnancy."

Volunteer Registry Database

For all studies involving greater than minimal risk, notification regarding the requirements of the Volunteer Registry Database, must be included in the consent form. The Volunteer Registry Database contains items of personal information, such as names, addresses, social security number, and the name of the respective study. Information in the database will only be disclosed in accordance with Army Regulation 340-21 (the Army Privacy Program) and the Privacy Act of 1974. This means that only a person for whom data is collected, or his/her designated agent or legal guardian may request information from the database. Only authorized staff of the Office of Regulatory Compliance and Quality have access to information stored in the database.

The USAMRDC Form 60-R must be completed for each volunteer. Send all completed forms to the Human Subjects Protection Branch annually and at the completion of the study. An example of the form is located in part 17 of this appendix. The following statement is normally included in the "Confidentiality" section of the consent form:

> "It is the policy of USAMRMC that data sheets are to be completed on all volunteers participating in research for entry into this Command's Volunteer Registry Database. The information to be entered into this confidential database includes name, address, social security number, study name, and dates. The intent of the data base is twofold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years."

9. Protocol Modifications and Amendments

As a second level review Board, the HSRRB continues to monitor protocols after the initial approval notification. All modifications to the protocol, consent form and/or questionnaires must be submitted to the HSRRB for review and approval prior to implementation. A list of proposed modifications or amendments to the protocol and an explanation of the need for these modifications should be submitted. The level of review required for approval depends on the nature of the modifications.

10. Continuing Review and Final Reports

All continuing review reports and the final report approved by the local IRB must be submitted to the HSRRB. A continuing review of the protocol must be completed by the local IRB at least once each year for the duration of the study.

11. Serious or Unexpected Adverse Event Reports

Include in the initial adverse event reports the name of the person submitting the report, if different from the PI, name of the study, the HSRRB log number (A-xxxx) assigned to the study,

the number of subjects enrolled to date, and the number and type of serious and unexpected adverse events previously reported in the study.

If the adverse event occurs in an IND study, the initial report must be identified as the "Initial Report for Subject (# or initials) enrolled in the clinical study Title and Log No. A-XXXX under IND #."

The following information must be provided:

(1) Description of Study. Double or single blind. If the study is being conducted in phases, indicate what phase of the study the subject is participating in.

(2) Number of subjects enrolled. Total enrollment at the time of the adverse event.

(3) Synopsis of event. Provide a complete narrative of the event.

(4) Subject status. Did the subject recover? What was the patient status at the time of the report?

(5) Other serious and unexpected adverse events from this study. Please provide any information pertaining to other adverse events that may have occurred during the conduct of this study.

(6) Most frequently expected adverse events based on the nature of the product. What adverse events would you expect to see based on the nature of the product or based on information contained in the most current version of the Investigator's Brochure.

(7) Actions taken in response to the adverse event. Is the subject still enrolled in the study or have they been dropped? Were any modifications or changes made to the protocol in response to the event? Provide an assessment of the relationship of the adverse event to the subject's participation in the study.

(8) Identification of the individual who completed the report. Include the signature, printed name and identity (investigator, study physician, etc.) of the individual who is providing the information.

In addition to the initial report of the adverse event, the report of the medical monitor must include his/her evaluation of the relationship of the adverse event to the subject's participation in the study and a follow-up report describing the resolution of the adverse event.

12. Assurances

If an institution has a current MPA or Cooperative Projects Assurance (CPA) with the DHHS Office for Human Research Protections, submit a letter with the following protocol information:

(a) MPA number, (b) risk level that the IRB classified the protocol (no greater than minimal risk or greater than minimal risk), (c) date of IRB approval, and (d) next continuing review date. This letter must be on official, institutional letterhead stationary and signed by the chairperson of the IRB that approved the protocol.

If the institution does not have a current MPA or CPA with the Office for Human Research Protections, a written Assurance of Compliance must be filed with the Human Subjects Protection Branch of the Office of the Deputy Chief of Staff for Regulatory Compliance and Quality. The obligation to obtain an assurance can be found in 32 CFR 219.103.

There are four requirements for a DOD SPA that must be submitted to the Human Subjects Protection Branch. The first is to complete a DOD SPA application. This application can be found at http://mrmc-www.army.mil/rcq/hspd.htm.

The second requirement is to provide a table of the IRB membership with the credentials (e.g. M.D., Ph.D., etc.) of each member with his or her affiliation with the institute and the role fulfilled on the IRB (e.g. chairperson, alternate, scientist, etc.). An example of this table is provided in the SPA application.

The third requirement is to provide short CVs or biographical sketches of all of the IRB members. These CVs are used to verify qualifications of the IRB members. The last requirement is to provide the written policies and procedures for conducting its initial and continuing review of research that are used by the IRB as outlined in 32 CFR 219.103. The SPA number will be issued after the protocol is approved by the HSRRB.

A letter from the Chairperson of the IRB that approved the protocol must accompany the SPA application on official, institutional letterhead stationary. The risk level assigned to the protocol by the IRB must be included along with the date of approval by the IRB and the next continuing review date.

13. Inclusion of Women and Minorities in Research

Consistent with the Belmont Report and recent congressional legislation, special attention is given to inclusion of women and minorities in research funded or managed by the USAMRMC. This policy is intended to promote equity both in assuming the burdens and in receiving the benefits of human subjects research. If women and/or minorities will be excluded from the protocol, a justification must be included.

14. Where to Go for Help and Information

If your research involves human subjects, you should first contact your local IRB for institutional requirements. If you have questions regarding the HSRRB protocol and consent form requirements or the review and approval process, contact the Office of Regulatory Compliance and Quality at the address or phone number listed below.

Phone: 301-619-2165/2166
Mail: Commanding General, U.S. Army Medical Research and Materiel Command

ATTN: MCMR-RCQ-HR
504 Scott Street
Fort Detrick MD 21702-5012

References:

- Title 32 Code of Federal Regulation, Part 219, Protection of Human Subjects
- Title 21 Code of Federal Regulation, Part 50, Protection of Human Subjects
- Title 21 Code of Federal Regulation, Part 56, Institutional Review Boards
- Title 21 Code of Federal Regulation, Part 312, Investigational New Drug Application
- Title 21 Code of Federal Regulation, Part 812, Investigational Devices
- Title 45 Code of Federal Regulation, Part 46, Subparts B, C, and D, Protection of Human Subjects
- Code of Federal Regulations is located at http://www.access.gpo.gov/nara/cfr/index.html
- Army Regulation 70-25, Use of Volunteers as Research Subjects
- Army Regulation 40-7, Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances
- Army Regulations can be located at http://www.usapa.army.mil
- Office of The Surgeon General Regulation 15-2, Human Subjects Research Review Board
- Title 10 United States Code, Section 980
- Department of Defense Directive 3216.2
- International Conference on Harmonisation, Good Clinical Practice, Consolidated Guideline is located at http://www.ifpma.org/pdfifpma/e6.pdf; all other ICH guidelines can be found in the ICH home page located at http://www.ifpma.org/ich1.html

Copies of the preceding references can be obtained from either the U.S. Government Printing Office or the National Technical Information Service at:

Phone: 202-512-1800
Web Site: http://www.access.gpo.gov/su_docs
Mail: Superintendent of Documents
P.O. Box 371954
Pittsburgh, PA 15250-7954

Phone: 703-605-6000; 800-553-NTIS
E-mail: orders@ntis.fedworld.gov
Mail: National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161

15. Claim of Exemption Form

PROTOCOL TITLE:	
PRINCIPAL INVESTIGATOR'S NAME:	PROPOSAL NO:
INSTITUTION:	

1. Will existing or archived data, documents, medical records, or database records be used? Yes No

2. Will biological specimens (e.g., cells, tissues, blood) be used? Yes No

3. Indicate below the sources of existing or archived data or biological specimens or cell lines (e.g., cell lines purchased from ATCC).

_____

_____

4. Will the donors of the original biological specimens be able to be identified, directly or indirectly, through identifiers linked to the donor? Yes No

5. Will data be recorded in writing? Yes No

6. Will data be recorded by audiotape? Yes No

7. Will data be recorded by videotape? Yes No

8. If survey instruments are used, will sensitive or private topics be explored? Yes No

9. Will subjects be identifiable either by name or through demographic data? Yes No

If the answer to any question 4-9 is yes, describe on a separate sheet of paper how the confidentiality of a subject's identity will be maintained. Also describe plans for maintaining or destroying identifying links to subjects after the protocol has been completed.

_____

Principal Investigator's Signature Date

16. Protocol Submission Checklist

PROTOCOL TITLE:	
PRINCIPAL INVESTIGATOR'S NAME:	PROPOSAL NO:
INSTITUTION:	

Requirement for All Protocols as Appropriate:

___ Research Protocol

___ Consent Form(s)

___ Curriculum Vitae or Biosketch for Principal Investigator and Medical Monitor

___ Documentation of the most current ethics training for all research staff

___ Scientific Review/Peer Review Approval(s)

___ Letter from the IRB Chairperson with the following protocol information: (a) MPA number, (b) risk level that the IRB classified the protocol (exempt, NGTMR, GTMR), (c) date of IRB approval, (d) next continuing review date, and (e) risk for medical devices (nonsignificant risk or significant risk).

___ Recruitment advertisements, posters, and announcements

___ Case report form(s), data collection/recording form(s), questionnaires, interview guides, etc.

___ Radiation Control Committee/Biosafety Review Report

___ Data Collection Forms and Case Report Forms

___ If potential commercial use of sample(s) or future use of sample(s) in other studies, a Sample Donation is required to be in the consent form.

___ With HIV Testing, documentation of consent for HIV antibody testing, if scheduled, may be addressed in the body of the consent form or as separate HIV test consent form.

Additional Requirements for IND Protocols:

___ Documentation of the Investigator's most recent GCP training

___ Document specifying IND Number

___ Investigator's Brochure

___ Copy of Case Report Forms (blank)

Protocol Submission Checklist (cont.)

Additional Requirements for Medical Device Protocols:

___ Documentation of the Investigator's most recent GCP training

___ Document from manufacturer declaring level of risk for device (non-significant risk or significant risk) and IDE form

___ Document specifying IDE Number

___ Manufacturer's device manual/ device information

What type of study is proposed?

___	Phase I Clinical Trial	___	Survey/Medical Record Review	___	Community Intervention
___	Phase II Clinical Trial	___	Cohort (longitudinal study)	___	Laboratory Experiment
___	Phase III Clinical Trial	___	Retrospective (case-control)	___	Tissue Only
___	Multicenter Trial	___	Program/Policy Study	___	Qualitative Study
___	Pilot Study	___	Cross-Sectional (prevalence)	___	Other: _____

Check all procedures applicable to this protocol:

___	Experimental Drug/Medications IND#_____	___	Prosthetic Orthopedic Devices
___	Marketed Agent, but Unapproved Use IND# _____	___	Nutrition/Metabolism Study
___	Experimental Device, IDE# _____	___	Tissue/Organ Transplant
___	Immunological Study	___	Radiation or Radioactive Material
___	Artificial Organ Study	___	Human Embryos
___	Experimental Treatments	___	Diagnostic Procedures
___	Experimental Surgery	___	Anatomical Substances Biological Specimens

Other: _____

Drug (s) to be used: _____ Drug Type* _____
_____ _____
_____ _____

*Drug Type may be chosen from the following list or other type may be stated as appropriate:

Analgesics	Anti-cancer drugs	Cardiac drugs	Hematologic agents
Anesthetics	Anti-convulsants	Diuretics	Hormones
Anti-allergy drugs	Anti-hypertensive drugs	Drugs affecting respiration	Tranquilizers/psychotopic drugs
Anti-arrhythmic drugs	Anti-Parkinson agents	Eye/Optical drugs	Vitamins/Minerals
Antibiotics/anti-infective agent	Autonomic drugs	Gastrointestinal drugs	

Protocol Submission Checklist (cont.)

Human Subject Information:

Age range of subjects: _____

Total number of subjects expected to be enrolled: _____

Total number of subjects at each collaborating site:_____

Check all that apply:

Subject Gender:
___Male
___Female

Are subjects able to provide their own consent?
___Yes
___No

Vulnerable Subject Class:
___Prisoners
___Minorities
___HIV positive
___Psychologically impaired
___Impaired decision-making
___Psychiatric patient
___Military
___Employee/Student
___Trauma

Subject Recruitment:
___In-patients
___Out-patients
___Students/employees
___Paid volunteers

Other:

_____

Principal Investigator's Signature

17. USAMRDC Form 60-R

VOLUNTEER REGISTRY DATA SHEET (USAMRDC 60-R)

THIS FORM IS AFFECTED BY THE PRIVACY ACT OF 1974

1. **AUTHORITY: 5 USC 301; 10 USC 1071-1090; 44 USC 3101; EO 9397**

2. **Principal and Routine Purposes: To document participation in research conducted or sponsored by the U.S. Army Medical Research and Materiel Command. Personal information will be used for identification and location of participants.**

3. **Mandatory or Voluntary Disclosure: The furnishing of the SSN is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide information may preclude your participation in the research study.**

PART A - INVESTIGATOR INFORMATION
(To Be Completed By Investigator)

PLEASE PRINT, USING INK OR BALLPOINT PEN

1. Study Number:_____ **2. Protocol Title:**

3. Contractor (Laboratory / Institute Conducting Study):

4. Study Period: From: _____/_____/_____ To: _____/_____/_____
DD MM YY DD MM YY

5. Principal / Other Investigator(s) Names(s): **6. Location / Laboratory**

1. _____ _____/_____
2. _____ _____/_____
3. _____ _____/_____

PART B - VOLUNTEER INFORMATION
(To Be Completed by Volunteer)

PLEASE PRINT, USING INK OR BALLPOINT PEN

7. SSN: _____/_____/_____ **8. Name: _____**

9. Sex: M____F____ **10. Date of Birth: _____/_____/_____** **11: *MOS/Job Series_____** **12: Rank/Grade _____**

13. Permanent Home Address (Home of Record) or Study Location:

_____ _____
(Street) **(P.O. Box / Apartment Number)**

_____ _____ _____
(City) **(Country)** **(State)** **(Zip Code)**

Permanent Home Phone Number: _____

14. * Local Address (If Different From Permanent Address):

_____ _____
(Street) **(P.O. Box / Apartment Number)**

_____ _____ _____
(City) **(Country)** **(State)** **(Zip Code)**

Local Phone Number: _____

15. * Military Unit: _____ Zip Code: _____

Organization: _____ Post: _____ Duty Phone Number: _____

VOLUNTEER REGISTRY DATA SHEET (USAMRDC 60-R) (continued)

PART C - ADDITIONAL INFORMATION
(To Be Completed by Investigator)

PLEASE PRINT, USING INK OR BALLPOINT PEN

16. Location of Study: _____

17. Is Study Completed: Y: _____ **N:** _____

Did volunteer finish participation: Y: _____ **N:** ____ **If YES, date finished** _____/_____/_____
DD MM YY

If NO, date withdrawn: _____/_____/_____ **Reason Withdrawn:**
DD MM YY

18. Did any Serious or Unexpected Adverse Incident or Reaction Occur: Y: _____ **N:** _____ **If YES, Explain:**

19. * Volunteer Follow-up: _____

Purpose: _____

Date: _____/_____/_____ **Was contact made: Y:** _____ **N:** _____ **If no action taken, explain:**

20. * Hard Copy Records Retired: Place: _____ **File NR:** _____

21. * Product Information:

Product: _____

Manufacturer: _____

Lot #: _____ **Expiration Date:** _____

NDA #: _____ **IND/IDE #:** _____

***Indicates that item may be left blank if information is unavailable or does not apply. Entries must be made for all other items.**

When completed, a copy of this form should be sent to the address below:

Commander
U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RCQ-HR
Fort Detrick, MD 21702-5012